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Iodine-123-MIBG Imaging in Pheochromocytoma with Cardiomyopathy and Pulmonary Edema

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We encountered a patient with pheochromocytoma associated with a catecholamine-induced cardiomyopathy that developed recurrently bilateral and unilateral pulmonary edema. The diagnosis of pheochromocytoma was made by elevated plasma catecholamine levels and intense tumor [¹²³I]MIBG uptake and was confirmed at the time of surgery. The patient showed reduced myocardial [¹²³I]MIBG uptake with left ventricular dysfunction, and endomyocardial biopsy findings were consistent with the diagnosis of catecholamine-induced cardiomyopathy. After tumor resection, plasma levels of catecholamine were normalized, and pulmonary edema never recurred, although cardiac dysfunction did not show an improvement on echocardiography. Myocardial and lung [¹²³I]MIBG uptake increased when compared to uptake levels on preoperative scans, but myocardial uptake was still below normal. These findings indicated that over-secreted catecholamines influenced both the heart and lungs. Pheochromocytoma can induce cardiac and lung injuries, and [¹²³I]MIBG scanning may contribute not only to tumor characterization but also to assessing and monitoring the influence of catecholamines on the heart and lungs.

Key Words: pheochromocytoma; cardiomyopathy; pulmonary edema; iodine-123-metaiodobenzylguanidine

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Radiolabeled metaiodobenzylguanidine (MIBG), a structural analog of guanethidine, shares the same uptake and storage mechanisms as norepinephrine (1-4). For myocardial imaging, this agent is useful to assess cardiac adrenergic activity, and to explore neuronal norepinephrine uptake and storage functions (4). For tumor imaging, it can provide tissue characterization of adrenergic tumors, and positive tumor uptake has been documented in 87%-96% of patients with pheochromocytoma and neuroblastoma with extremely high specificity (5-8). Moreover, this agent is extracted in lung endothelium by the same active, sodium-dependent saturable transport system as norepinephrine (9-11).

In pheochromocytoma, over-secreted catecholamines can induce myocardial (12-17) and lung (14,18,19) injuries. MIBG scanning may become a unique procedure which allows detection of primary tumor as well as myocardial and lung abnormalities. In this paper, we present the findings of [¹²³I]MIBG

scan performed before and after tumor removal in a patient with pheochromocytoma associated with catecholamine-induced cardiomyopathy and lung edema.

CASE REPORT

A 70-yr-old woman consulted her private physician complaining of a cough and a low-grade fever for 2 wk, and was administered an intravenous drip infusion of 500 ml glucose 5%. During treatment, she complained of severe dyspnea and heart palpitations, and was admitted to the emergency room of our hospital. Seven months earlier, she had been hospitalized for paroxysmal, acute bilateral pulmonary edema, which disappeared rapidly in 3 days. At that time, coronary angiography demonstrated normal coronary arteries, and endomyocardial biopsy showed a mild focal interstitial infiltrate of lymphocytes with scanty myocytolysis; hence, she was diagnosed with myocarditis due to viral infection. She had never demonstrated hypertension.

On this admission, chest auscultation revealed widespread moist rales in the right lung. Blood pressure was 142/86 mmHg and pulse rate was 110/min. Arterial blood gases showed hypoxia with PO₂ levels of 36.2 mmHg. Electrocardiogram showed sinus tachycardia, but no evidence of myocardial infarction or left ventricular hypertrophy. Chest radiograph and chest and CT showed right unilateral lung edema, accompanied by moderate cardiomegaly with a cardiothoracic index of 56%. Color Doppler echocardiography showed left ventricular hypokinesis with a fractional shortening of 44% and a contractility of 25%, without significant left ventricular hypertrophy. The patient's condition improved rapidly following bed rest and diuretic therapy. Chest radiograph and CT on the third day revealed that the right lung edema had disappeared. Lung perfusion scan with ^{99m}Tc macroaggregated albumin (MAA) performed on the fifth day did not show any abnormality in either lung. The patient was subsequently discharged. Review of the patient's history and the above findings led to the diagnosis of acute unilateral lung edema due to left ventricular failure.

Fifteen days after discharge, however, she again complained of sudden dyspnea while working in her garden and was hospitalized again. The main Clinical data obtained at this admission are summarized in Table 1. She again showed hypoxia and right unilateral lung edema on chest radiograph (Fig. 1); however, these improved rapidly on the second day, following bed rest. Thereafter, she occasionally became unstable with a wild fluctuation in blood pressure. Serum levels of catecholamines were significantly elevated. Abdominal ultrasound and x-ray CT revealed a large, solid mass measuring 60 × 60 mm in diameter in the ventral region of

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TABLE 1
Summary of Clinical and Laboratory Data

Blood pressure	135/83 mmHg (temporarily, 80/42 to 210/110 mmHg)
Heart rate	96–110/min (temporarily, 135–146/min)
Arterial blood gases	PO ₂ 38.6 mmHg, PCO ₂ 32.4 mmHg
Serum catecholamine level	Norepinephrine 3550 pg/ml (normal values <400), Epinephrine 3080 pg/ml (normal values <40)
Echocardiography (Left ventricle)	Fractional shortening 43%, Contractility 25%

the left kidney (Fig. 2), which was homogeneously enhanced by contrast material. The left adrenal gland was not swollen, apart from the mass lesion. Planar [¹²³I]MIBG scanning was performed 8 days after admission using a gamma camera. At this time, she was normotensive (138/84 mmHg), and echocardiography showed left ventricular hypokinesis similar to the previous examination. She fasted and did not receive any drugs that could interfere with myocardial MIBG uptake, such as reserpine and tricyclic antidepressants. A dose of 111 MBq [¹²³I]MIBG was injected intravenously after a 30-min rest period. Anterior and posterior images were acquired at 30 min, 3 hr and 6 hr, all of which showed intense MIBG uptake in the abdominal mass (Figs. 2 and 3). Diagnosis of pheochromocytoma was confirmed, despite the rather unexpected location of the mass. On the serial images, regions of interest

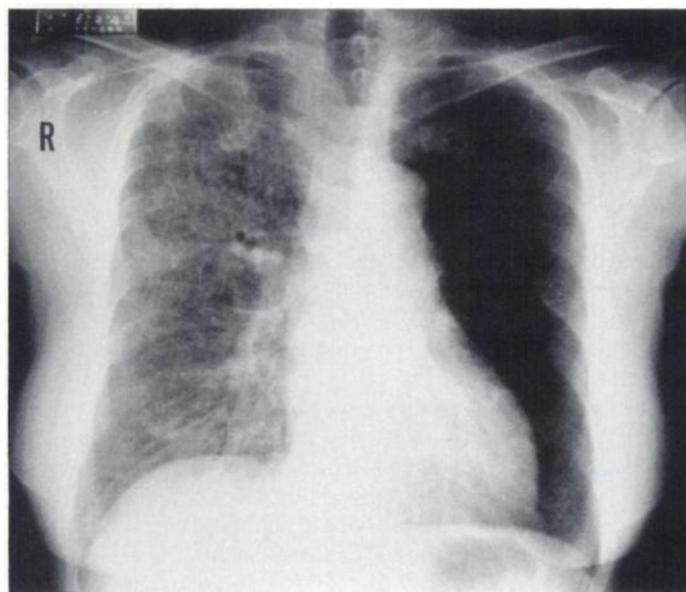


FIGURE 1. Admission posteroanterior chest radiograph shows unilateral pulmonary edema in the right lung.

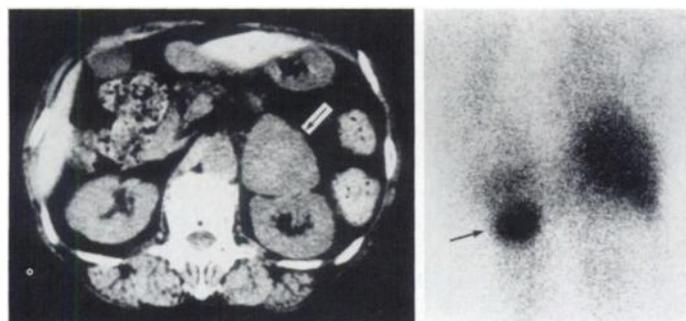


FIGURE 2. (A) Abdominal x-ray CT shows a large, solid mass measuring 60 × 60 mm in diameter in central region of left kidney (arrow). (B) Posterior view of preoperative [¹²³I]MIBG scan (6 hr postinjection) shows intense MIBG uptake corresponding to the mass (arrow).

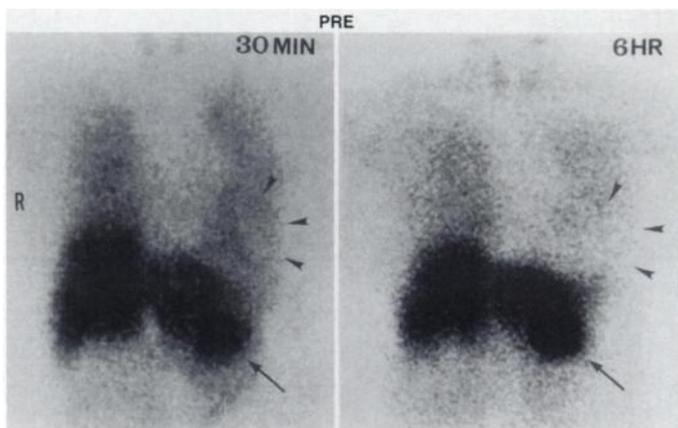


FIGURE 3. Preoperative [¹²³I]MIBG scans (anterior view, 30 min and 6 hr postinjection) show remarkably reduced myocardial MIBG uptake (arrowheads). Lung uptake is also reduced compared to that in normal subjects (Table 2). Intense uptake is seen in the pheochromocytoma mass below left hepatic lobe (arrows).

(ROIs) were manually set on the whole heart, and other squared ROIs of 4 × 4 pixels were placed over the upper mediastinum and upper lungs. The heart-to-mediastinum and lung-to-mediastinum ratios were calculated by the mean counts of one pixel of ROIs. Heart-to-mediastinum ratios in all serial images were lower than the mean ± 2 s.d. in eight healthy subjects (five males and three females, 61–75 yr-old) without evidence of cardiac or lung disease (Table 2). There was no difference in MIBG uptake between the two lungs, and while the lung-to-mediastinum ratio of the right lung was relatively low, it did not differ significantly from those in the eight healthy subjects (Table 2). The patient was referred for surgery, and an encapsulated mass measuring 59 × 57 mm in diameter was completely removed. Histological examination confirmed the diagnosis of pheochromocytoma. Immediately after surgery, serum levels of catecholamines returned to normal.

During the year following her surgery, the patient's blood pressure remained within normal limits, and lung edema never recurred. Follow-up [¹²³I]MIBG scanning (Fig. 4), performed 9 mo after surgery using the same procedures for the preoperative scan, depicted the myocardium more clearly than in the preoperative scan. The heart-to-mediastinum ratio increased (Table 3), but was still low compared to that of the healthy subjects, and echocardiography did not show any significant changes in left ventricular function, with a fractional shortening of 45% and a contractility of 25%. The lung-to-mediastinum ratio also increased when compared to that on the preoperative scan (Table 3).

DISCUSSION

This patient with pheochromocytoma had severe cardiac dysfunction and developed recurrent lung edema. Cardiac dysfunction due to catecholamine-induced cardiomyopathy is a well-known phenomenon in pheochromocytoma (12,15). This patient, however, had no history of chronic hypertension, and remained normotensive while her clinical status deteriorated. Her severe cardiac dysfunction may be attributed to lack of hypertension. Pheochromocytoma induces hypertension, but there is a distinct group of patients (up to 30%) who remain normotensive despite active secretion of catecholamine (12,13). High blood pressure sometimes returns to normal because of cardiac damage. Sardesai et al. (12) reported on six patients with pheochromocytoma that showed heart failure with or without lung edema, five of which were normotensive and suggested that catecholamine-induced cardiomyopathy in normotensive patients is more common than previously thought. This case, however, also had a short episode in which the

TABLE 2
Heart-to-Mediastinum and Lung-to-Mediastinum Ratios in Healthy Subjects and Patient

	Heart-to-mediastinum ratio			Lung-to-mediastinum ratio		
	30 min	3 hr	6 hr	30 min	3 hr	6 hr
Healthy subjects (mean ± s.d., n = 8)	2.51 ± 0.25	2.73 ± 0.24	2.65 ± 0.22	1.82 ± 0.17	1.56 ± 0.20	1.52 ± 0.18
Reported patient	1.73	1.32	1.17	1.71	1.52	1.45

patient's blood pressure fluctuated wildly. In patients presenting with paroxysmal symptoms or heart failure without any obvious causes (chronic hypertension or ischemic heart disease), diagnosis of pheochromocytoma should be considered (12-15). Acute lung edema is also a known but rare feature of pheochromocytoma (12,13,15,20). Cardiac injury causes lung edema (12-15,20), but noncardiogenic factors associated with local effects of excess catecholamine on the lungs can also cause it (18,19). In fact, lung edema was seen in a pheochromocytoma patient without cardiac dysfunction (14). This type of edema is caused by transudation of fluid in the alveoli or interstitial space, which is induced by both an increase in the pulmonary-capillary hydrostatic pressure due to constriction of postcapillary vessels and lymphatic channels, and by increased microvascular permeability (18,19). In this case, when considering the unchanged cardiac dysfunction after surgery, both factors seem to have caused lung edema. The preoperative, reduced lung MIBG uptake may be partially related to lung damage (9,14,18,19). Unilateral lung edema in this case was unusual. It occurs most commonly in patients with cardiac decompensation who are in a dependent position (21,22), and also in those with perfusion defects or impaired vascular permeability in one lung only (21). This case, however, had no abnormalities in lung vasculature on chest x-ray, CT or ^{99m}Tc-MAA scan. Therefore, we cannot confidently determine the etiology. Unilateral edema, however, does occur more fre-

quently in the right than in the left lung (22). The right lung may have anatomical and functional factors that easily manifest edema; for instance, there is a difference in lymphatic drainage. Lymphatic channels in the right lung frequently form a tracheo-mediastinal truncus, whereas in the left lung, the channels tend to individually drain into the truncus thoracicus (22).

The mechanisms of reduced myocardial MIBG uptake in pheochromocytoma may be multifactorial. First, it is related to a catecholamine-induced cardiomyopathy. As a direct effect of excess catecholamine on the myocardium, focal myofibril degeneration with inflammatory cellular infiltrations has been demonstrated in both animal and human studies (12-17,23,24). This patient's histology is consistent with this finding, although it resembles viral myocarditis (12,23). Myocardial cell damage is due to reduced coronary perfusion and hypoxia caused by vasospasm that is mediated by an adrenergic receptor (25) and a change in calcium permeability in the cell membrane (12). There is also evidence that oxidized catecholamine products are toxic (14). Functionally, excess norepinephrine leads to a reduction in global myocardial pump function (26). These pathological and functional damages can result in heart failure, which itself results in decreased myocardial norepinephrine content and MIBG uptake unrelated to the etiology (1,3). In fact, these decreased uptake levels are due to a decreased number of sympathetic nerve endings (2,3), impaired neuronal uptake function (4), decreased density of sympathetic nerves due to ventricular enlargement and reduced synthesis of norepinephrine or rapid turnover of catecholamine in the neurons (4,27). As a second factor in reduced MIBG uptake, competition of MIBG with excess catecholamine at the receptor site has been considered. Nakajyo et al. (27) found an inverse relationship between myocardial MIBG uptake and plasma catecholamine in pheochromocytoma patients. Reduced uptake was seen in a patient with neuroblastoma and an increase in norepinephrine, but without heart dysfunction (7). Thus, reduction can occur in a patient without cardiac injury, and in non-pheochromocytoma patients with elevated plasma catecholamine (27). In this case, both factors may have caused reduced MIBG uptake, because the uptake increased preoperatively, despite the lack of change in cardiac dysfunction. The persistent low MIBG uptake after surgery may reflect severe cardiac dysfunction and long-term evolution of damage. Although catecholamine-induced cardiomyopathy can be reversible after removal of the tumor (13-15,20,28,29), reversibility

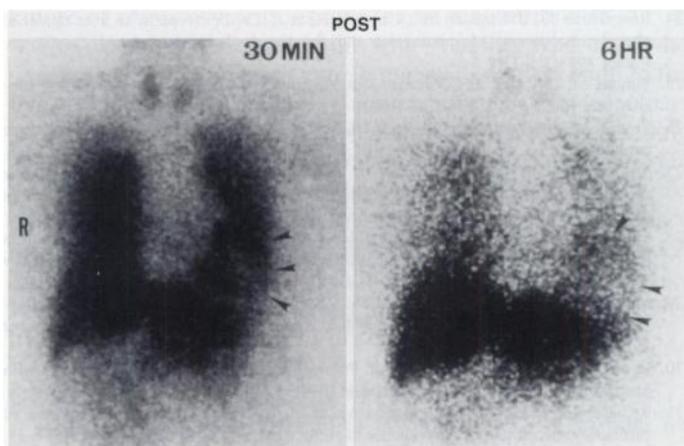


FIGURE 4. Iodine-123 MIBG scans (30 min and 6 hr postinjection) performed 9 mo after surgery show increased [¹²³I]MIBG uptake in both the myocardium (arrowheads) and in the lungs compared to that on preoperative scans (Fig. 3).

TABLE 3
Comparison of Pre- and Postoperative Heart-to-Mediastinum and Lung-to-Mediastinum Ratios

	Heart-to-mediastinum ratio			Lung-to-mediastinum ratio		
	30 min	3 hr	6 hr	30 min	3 hr	6 hr
Preoperation	1.73	1.32	1.17	1.71	1.52	1.45
Postoperation	1.78	1.68	1.60	2.01	1.86	1.57

and time to normalization depend on the duration and severity of dysfunction (14).

This patient showed reduced lung [^{123}I]MIBG uptake preoperatively, despite the presence of cardiac dysfunction, while patients with heart failure usually show high uptake (30). This reduction is considered due to lung damage induced by excess catecholamine and competition with excess norepinephrine. MIBG extraction in lung endothelium involves the same saturable, energy-requiring, sodium-dependent transport system as norepinephrine (9–11). Therefore, this agent can detect endothelial damage, because injured endothelium show a decreased ability to extract norepinephrine (9). This agent also shows competition with norepinephrine in lung extraction. Slosman et al. (10,11) showed reduced lung MIBG uptake in bleomycin-treated rat lungs and in sheep lungs with endotoxemia, both of which showed morphological changes in endothelial cells only (9), and in rat lungs administered norepinephrine (10,11). Richalet et al. (31) also showed reduced lung uptake in response to prolonged hypoxia, which induced endothelial damage and increased plasma norepinephrine. The improved MIBG lung uptake after surgery in the present patient may have been due to the recovery of lung damage and/or withdrawal of excess catecholamine. We have also encountered a 7-yr-old child with neuroblastoma whose lung MIBG uptake increased when tumor size and plasma catecholamine levels were reduced after chemotherapy. Thus, in a patient with catecholamine-producing tumors, MIBG seems to have the potential to evaluate the influence of excess catecholamine on the lungs.

Thus, we should remember that pheochromocytoma can be associated with cardiac and lung injuries. Pheochromocytoma should be considered in patients with paroxysmal symptoms or heart failure without other obvious cause, even in normotensive patients. Normotensive patients may be more likely to die as a result of cardiac injury and lung edema because the diagnosis may not be suspected (12,14). Noninvasive MIBG imaging is useful in the detection of primary tumors in patients suspected of pheochromocytoma (5–8). Furthermore, measuring cardiac and lung MIBG uptake is useful in detecting cardiac and lung injuries induced by excess catecholamine. Catecholamine-induced cardiomyopathy can be improved or reversed by removal of the tumor (14,15,20,28,29), or by medication with alpha-adrenergic blockers or captopril (13). Therefore, early diagnosis can prevent such fatal events. Moreover, preoperative assessment of underlying catecholamine-induced changes in heart and lung will help prevent perioperative heart failure and lung edema (32). This modality may also be useful for evaluating the reversibility of cardiac and lung damage after surgical or medical treatment of tumors.

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